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Ambient Water Quality Criteria Vinyl Chloride

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VINYL CHLORIDE

Ambient Water Quality Criteria

Criteria and Standards Division
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CRITERION DOCUMENT

VINYL CHLORIDE

CRITERIA

Aquatic Life

For freshwater aquatic life, no criterion for vinyl chloride can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for vinyl chloride can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to vinyl chlorides through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of vinyl chloride estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 517 µg/l, 51.7 µg/l, and 5.17 µg/l, respectively.

BIBLIOGRAPHIC INFORMATION

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Ambient Water Quality Criteria: Vinyl Chloride.

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for vinyl chloride. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself h , ...

KEYWORDS: *Water quality, *Toxicology, *Vinyl chloride, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Ethylene/chloro.

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Introduction

Vinyl chloride has been used for over 40 years in producing polyvinyl chloride (PVC) which in turn is the most widely used material in the manufacture of plastics throughout the world. Of the estimated 18 billion pounds of vinyl chloride produced worldwide in 1972, about 25 percent was manufactured in the United States (Berk, et al. 1976). Production of vinyl chloride in the United States reached slightly over 5 billion pounds in 1977 (U.S. Int. Trade Comm). Production of vinyl chloride has risen nearly 14 percent annually between 1968 and 1973 as evidenced by the broad dependence of nearly every branch of industry and commercial activity upon products and components fabricated from polyvinyl chloride (U.S. EPA, 1974).

Vinyl chloride and polyvinyl chloride are used in the manufacture of numerous products in building and construction, the automotive industry, for electrical wire insulation and cables, piping, industrial and household equipment, packaging for food products, medical supplies, and is depended upon heavily by the rubber, paper and glass industries (Maltoni, 1976). Polyvinyl chloride and vinyl chloride copolymers are distributed and processed in a variety of forms including dry resins, plantisol (dispersions in plasticizers), organososl (dispersions in plasticizers plus volatile solvent), and latex (colloidal dispersion in water). Latexes are used to coat or impregnate paper, fabric, or leather (Falk, et al. 1974).

As of 1974, approximately 15 plants synthesized the vinyl chloride monomer, 43 facilities were engaged in the polymerization of PVC and over 7,500 plants fabricated products from PVC. About 1,500 workers were employed in monomer synthesis and an additional 5,000 in polymerization operations (Falk, et al. 1974). As many as 350,000 workers were estimated to be associated with fabrication plants (U.S. EPA,1974). By 1976 it was estimated that nearly one million persons were associated with manufacturing goods derived from PVC (Maltoni, 1976).

Vinyl chloride levels ranging from barely detectable to high concentrations have been found in drinking water, beverages, food, cosmetics, and other consumer products. Aerosol products containing vinyl chloride as a propellant have been discontinued. However, incinerators may be an additional source of vinyl chloride emissions since the entrapped monomer escapes following incomplete combustion of PVC products. Insufficient published data are available on exposure levels of persons living in the vicinity of PVC fabricating plants, or on the release of the monomer from various plastic products. However, all of these routes represent additional potential sources of population exposure (U.S. EPA, 1975).

Vinyl chloride (CH_2CHCl; molecular weight 62.5) is a highly flammable chloroolefinic hydrocarbon which emits a sweet or pleasant odor and has a vapor density slightly more than twice that of air (Weast, 1972; Braker and Mossmein, 1971). It has a boiling point of -13.9 degrees C and a

melting point of -153.8 degrees C. Its solubility in water at 28 degrees C is 0.11 g/100g water and it is soluble in alcohol and very soluble in ether and carbon tetrachloride (Weast, 1972). Vinyl chloride is volatile and readily passes from solution into the gas phase under most laboratory and ecological conditions. Many salts such as soluble silver and copper salts, ferrous chloride, platinous chloride, iridium dichloride, and mercurous chloride to name a few, have the ability to form complexes with vinyl chloride which results in its increased solubility in water. Conversely, alkali metal salts such as sodium or potassium chloride may decrease the solubiltiy of vinyl chloride in aqueous ionic strength of the solution (Fox, 1978). Therefore, the amounts of vinyl chloride in water could be influenced significantly by the presence of salts (U.S. EPA, 1975a).

The large quantities and widespread use of vinyl chloride in the production of PVC, together with recent evidence of occupational hazards resulting from polymerization operations has caused concern for the protection of workers and the environment. Thus far, the principal route of exposure to people working in or living near vinyl chloride industries is thought to be air inhalation. However, the discharge of water used in the polymerization process has become of increased importance as a source of contamination to the aquatic environment and exposure to the public in general. Additional exposure can occur via ingestion of contaminated food and through the skin (U.S. EPA, 1975).

There are no aquatic toxicity data available in the scientific literature at the present time. A combination of vinyl chloride's known toxicity via inhalation and its low water solubility makes testing this compound extremely dangerous and difficult. Vinyl chloride has been shown to be toxic to experimental animals and numerous studies have reported its carcinogenic effects in rats, mice, hamsters and rabbits. Vinyl chloride has been shown only recently to be an occupational hazard, resulting in the development of vinyl chloride disease. The disease represents a multi-system disorder incorporating acroosteolysis, a skin disorder characterized by Raynaud's phenomenon, thrombocytopenia, portal fibrosis, and hepatic and pulmonary dysfunction. In addition, there is evidence that workers involved in the polymerization of vinyl chloride monomer show a higher incidence of angiosarcoma, one of the rarest human malignant neoplasms (Filatova and Gronsberg, 1957).

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AQUATIC LIFE TOXICOLOGY

No appropriate data are available for freshwater or saltwater organisms and vinyl chloride. One paper by Brown, et al. (1977) described an acute test using northern pike but the description of test methods was incomplete and the control organism procedures were quite different from those for the exposed organisms.

CRITERION FORMULATION

No freshwater or saltwater criterion can be derived for vinyl chloride using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Introduction

Sufficient evidence has been accumulated in recent years implicating vinyl chloride as a human and animal carcinogen. The first four human cases of liver angiosarcoma in workers employed by a vinyl chloride plant were reported by Creech and Johnson in 1974. The first experimental data on the carcinogenic effects of vinyl chloride in rats were published by Viola, et al. in 1971; a comprehensive report on dose-effect relationship of vinyl chloride in experimental animals by Maltoni, et al. followed in 1974. These initial reports spurred a series of retrospective epidemiologic investigations of workers in the vinyl chloride industry and supportive experimental studies in animals. The large amount of published literature was summarized in several comprehensive reviews; of note are the two volumes compiled by the New York Academy of Sciences in 1975 and 1976, a review in the Proceedings of the Royal Society of Medicine (1976) and the U.S. EPA Scientific and Technical Assessment Report (STAR) on Vinyl Chloride and Polyvinyl Chloride (1975a).

The purpose of this report is to briefly summarize the published reviews and reports including more recently published data with special attention to research studies concerned with the extent of human exposure to vinyl chloride contaminated public water supplies. Unfortunately, toxicologic or epidemiologic data on this issue are not

available, since vinyl chloride appears to escape in gaseous phase from surface waters; only one report was located indicating the presence of small amounts of vinyl chloride in water supplies of two cities. There is scanty information available on the carcinogenic effects of vinyl chloride due to ingestion of vinyl chloride-contaminated olive oil (Maltoni, 1976).

Vinyl chloride is not found in nature. It is synthesized as chlorinated olefinic hydrocarbon monomer derived from petrochemical feedstock and chlorine. Vinyl chloride emissions to the U.S. environment originate from three major sources: (1) 17 existing plants where vinyl chloride is commercially synthesized (about 11 percent); (2) 41 existing polyvinyl chloride (PVC) plants where the vinyl chloride monomer is used in the products of PVC resins for various industrial purposes (about 35 percent); (3) some 8,000 PVC fabricating plants and other miscellaneous sources. 40 FR 59534 (December 24, 1975). In 1974, the U.S. production of PVC was over 4 billion pounds. Emissions from these sources, therefore, present the primary risk of vinyl chloride exposure for workers employed in these industries and populations living in their vicinity; however, additional exposure, even though it is thought to be minimal, can occur via ingestion of contaminated food and water, and through the skin. Vinyl chloride levels from detectable to high have been found in drinking water, beverages, food, cosmetics, and other consumer products. Aerosol products containing vinyl chloride as a propellent have been discontinued. Municipal incinerators may be an additional source of vinyl chloride emissions

as the entrapped monomer escapes following incomplete combustion of PVC products. Insufficient published data are available on exposure levels of persons living in the vicinity of PVC fabricating plants, or on the release of the monomer from various plastic products. Yet, all of these are additional potential sources of population exposure.

Ingestion from Water

Small amounts of vinyl chloride may be present in public water supplies as a result of vinyl chloride industrial waste water discharges. Levels of vinyl chloride in waste water effluents vary considerably depending on the extent of in-plant treatment of waste water. Vinyl chloride in samples of waste water from seven areas (representing 12 PVC-vinyl chloride plants) ranged from 0.05 ppm to 20 ppm (U.S. EPA, 1974). More typically, levels of 2 to 3 ppm were found. In these studies, values represent vinyl chloride concentrations in three 24-hour composite waste water samples. The low solubility and high volatility of vinyl chloride in water (0.11 percent) limits the amount present in a given volume; however, the presence of other agents, such as salts, increases the solubility of vinyl chloride and therefore could create situations of concern (U.S. EPA, 1975a).

Polyvinyl chloride pipe used in water distribution systems provides another source of low levels of vinyl chloride in drinking water. The U.S. EPA's Water Supply Research Division studied five water distribution systems which used PVC pipes (Dressman and McFarren, 1978). Sites chosen were representative of extremes in climatic conditions and of

variable age, length, and size of pipes. Low concentrations of vinyl chloride were detected in three of the five water supply systems. Water from the most recently installed and the longest pipe system had the highest vinyl chloride concentration (1.4 μg/l). Traces of vinyl chloride (0.03 and 0.06 μg/l) were still present in the other two systems (which were the oldest), about 9 years after installation.

The National Science Foundation (NSF) annually issues a list of PVC pipe and fittings conforming to standard No. 14. Those manufactured in 1977-78 and listed will be low in residual monomer. A level of 10 ppm or less of residual monomer in finished pipe and fittings was adopted as a voluntary standard in February, 1977. Three times a year NSF field personnel collect test samples. More than 95 percent of these samples conformed to the standard in 1977. However, in testing samples of water supplies in several cities, vinyl chloride (5.6 μg/l and 0.27 μg/l) has been detected in the water supply of at least two American cities (U.S. EPA, 1975b).

Although the vinyl chloride concentrations in public water supplies tested so far are below the minimum levels associated with reported carcinogenic or other toxic responses, confirmation studies with experimental animals are in progress. For example, investigations are being conducted by Professor Cesare Maltoni of Bologna, Italy, to determine the incidence and type of cancer produced by ingestion of low doses of vinyl chloride, including 1.0, 0.3, and 0.03 mg/kg/day. Because of the long latency of the carcinogenic response, the results of these investigations will not be available for some time (Maltoni, 1976).

The environmental fate of vinyl chloride was evaluated in a closed model aquatic ecosystem by Lu, et al. in 1977. Five organisms, including algae and fish, bioaccumulated small amounts of vinyl chloride and/or metabolites of vinyl chloride. The low tissue values observed in fish as a result of the three day exposure suggest that vinyl chloride is not biomagnified to any great degree.

Ingestion from Food

Small quantities of vinyl chloride are ingested by humans since the entrained monomer migrates into foods packaged in PVC wrappings and containers. The solubility of vinyl chloride in foods packaged in water is low (0.11 percent); however, the monomer is soluble in alcohols and mineral oil. In 1973, prior to the recognition of the carcinogenicity of vinyl chloride in man, the U.S. Treasury Department banned the use of vinyl chloride polymers for packaging alcoholic beverages as a result of studies indicating that levels up to 20 mg/kg were present in liquors so packaged (Int. Agency Res. Cancer, 1974). The reason for this action was that vinyl chloride migration into the liquor resulted in a discoloration and unpleasant taste. The Food and Drug Administration analyzed a number of PVC packaged products for vinyl chloride content in 1974. Concentrations ranged from "not detectable" to 9,000 ppb. Vegetable oils and apple cider contained the highest concentration.

Withey and Collins (1976) have developed a statistical model for use in equating oral dose levels of vinyl chloride to inhalation exposure levels in rats, using vinyl chloride blood level time curves. For example, the authors concluded that "if the total daily liquid intake contained 20 ppm

vinyl chloride, then the area generated under the blood level time curve for rats would be equivalent to an inhalation exposure of about 2 ppm for 24 hours".

A bioconcentration factor (PCB) relates the concentration of chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

No measured steady-state bioconcentration factor (BCF) is available for vinyl chloride, but the equation "Log BCF = 0.76 Log P - 0.23" can be used (Veith, et al. Manuscript) to estimate the BCF for aquatic organisms that contain about 8 percent lipids from the octanol-water partition coefficient (P). Based on an octanol-water partition coefficient of 24, the steady-state bioconcentration factor for vinyl chloride is estimated to be 6.6. An adjustment factor of 2.3/8.0 = 0.2875 can be used to adjust the estimated BCF from the 8.0 percent lipids on which the equation is based to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for vinyl chloride and the edible portion of all aquatic organisms consumed by Americans is calculated to be 6.6 x 0.2875 = 1.9.

Inhalation

Inhalation of vinyl chloride is the principal route of exposure to people working in or living near vinyl chloride industries. Vinyl chloride boils at -13.9°C and is a gas at normal atmospheric temperature and pressure. The odor is usually described as sweet or pleasant and those familiar with the odor may first detect it at 1,200 to 2,000 ppm.

Because of its narcotic properties (Patty, et al. 1930), vinyl chloride was considered for use as an anesthetic agent, but reports in 1947 of cardiac arrythmias in dogs following its inhalation resulted in vinyl chloride being dropped from consideration as an anesthetic (Oster, et al. 1947).

Relatively little attention was given in the past to monitoring vinyl chloride in the air of workplaces because toxicologic data at the time indicated there was little hazard. The earliest reports of hepatoxicity in vinyl chloride workers were noted by Tribukh, et al. (1949); however, the effects were attributed to plasticizers added in the manufacturing process. In these studies, the observed concentrations of vinyl chloride ranged from 1 to 470 ppm.

Some data are available concerning airborne vinyl chloride in the workplace prior to 1974. In Russia, Filatova and Gronsberg (1957) observed concentrations of 8 to 16,000 ppm with average exposures ranging from 20 to 300 ppm. Although monitoring of the workplace for vinyl chloride levels was not a common practice, in the U.S. prior to 1950, Dow Chemical Co. initiated monitoring about that time. Exposures were generally below 500 ppm; however, peak concentrations of 4,000 ppm were recorded (Ott, et al. 1975). After 1960, Dow Chemical Co. was successful in reducing exposures to workers to about 25 ppm even though levels up to 500 ppm still occurred. After vinyl chloride-induced angiosarcoma of the liver was reported in workers and animals (Creech and Johnson, 1974; Viola, et al. 1971; Maltoni and Lefemine, 1974a) inhalation exposures dropped drastically.

Inhalation of vinyl chloride by the general population occurs in the vicinity of vinyl chloride and PVC industries. This problem currently is receiving increased attention. Prior to 1974, vinyl chloride was widely used as a propellant for many commercially available products such as pesticides, deodorants, hair sprays, etcetera. Consumers repeatedly using such products in closed rooms were undoubtedly exposed to moderately high concentrations.

Dermal

Absorption of vinyl chloride through the skin is minor. Calculations based on the percutaneous absorption of vinyl chloride by Rhesus monkeys (Hefner, et al. 1975b), indicate that a 6-foot, 90 kg man exposed to 7,000 ppm (dermal) for 2 hours would absorb the equivalent of a 0.2 ppm, 8-hour inhalation exposure. Therefore, significant percutaneous

absorption would not be expected to occur upon exposures to low concentrations of 1 or 5 ppm.

PHARMACOKINETICS

Absorption

Vinyl chloride is rapidly absorbed through the lungs and enters the blood stream (Duprat, 1977). In rats inhaling 20,000 ppm (^{14}C) vinyl chloride for 5 minutes, ^{14}C was found in the liver, bile duct, digestive lumen, and kidneys 10 minutes from the beginning of the inhalation exposure. The amount and distribution of vinyl chloride and its metabolites increased up to 3 hours post-exposure and in addition to sites of deposition observed 10 minutes from initiation of exposure, ^{14}C activity was found in the urinary tract, salivary, harder and lacrimal glands, skin, and thymus. Watanabe, et al. (1976b) and Bolt, et al. (1977) also observed the rapid uptake and equilibration of atmospheric vinyl chloride with rats via the inhalation route.

The fate and absorption of vinyl chloride following oral administration is consistent with observations derived from inhalation studies (Watanabe, et al. 1976a). Watanabe, et al. (1977) compared the fate of vinyl chloride in rats following repeated versus single inhalation exposures in rats and found that the routes and rates of excretion were the same for both groups. The activity of microsomal enzymes was essentially the same in rats exposed once, repeatedly, and in control rats. Covalent bonding to hepatic macromolecules was greater in repeatedly exposed rats than in those given a single exposure. The hepatic nonprotein sulfhydryl concentration of the repeatedly exposed rats was greater than the single exposure rats (79 and 37 percent

of control, respectively); the authors conclude that "...repeated exposure to vinyl chloride does not induce its biotransformation. However, the increase in hepatic macromolecular binding indicates that repeated exposure augments the reaction of electrophilic metabolites with macromolecules, and this may be expected to enhance potential toxicity including carcinogenicity."

Using male Wistar rats, Withey (1976) determined that vinyl chloride migrates rapidly from the gastrointestinal tract to the blood following gastric intubation of aqueous solutions of vinyl chloride (22.6 to 28.2 mg per animal) or gastric intubation of a vegetable oil solution of vinyl chloride (12.55 or 25.1 mg per animal). The nature of the vehicle had little or no effect on the rates of uptake or elimination kinetics. After a 5 hour inhalation exposure at approximately 7,000 ppm, blood levels of vinyl chloride decreased rapidly.

Distribution

The liver of rats (Table 1) retains the greatest percentage of vinyl chloride and/or metabolites of vinyl chloride 72 hours after single oral administration of 0.05, 1.0 or 100 mg/kg of the ^{14}C-labeled compound (Watanabe, et al. 1976a).

Ten minutes after the initiation of a 5 minute 10,000 ppm inhalation exposure to ^{14}C-vinyl chloride, ^{14}C activity is found in the liver, bile duct, stomach, and kidneys of rats (Duprat, 1977).

Bolt, et al. (1976) studied the tissue disposition of ^{14}C-vinyl chloride in rats. Immediately after exposure by inhalation of 50 ppm vinyl chloride for 5 hours in a

closed system, the percent incorporated as ^{14}C-radioactivity per g tissue was highest for kidney (2.13), liver (1.86), and spleen (0.73). Forty-eight hours after the beginning of exposure, labeled material could still be detected in these tissues.

Metabolism

Detoxification of vinyl chloride takes place primarily in the liver by oxidation to polar compounds which can be conjugated to glutathione and/or cysteine (Hefner, et al. 1975a). These covalently bound metabolites are then excreted in the urine.

Vinyl chloride is metabolized extensively by rats in vivo and the metabolic pathway appears to be saturable (Watanabe, et al. 1976a, b; Bolt, et al. 1977; Hefner, et al. 1975a). These investigators postulate that the primary metabolic pathway involves alcohol dehydrogenase because ingested ethanol or pyrazole inhibits the uptake of vinyl chloride. In rats this primary pathway appears to be saturated by exposures to concentrations exceeding 220 to 250 ppm. In rats exposed to higher concentrations, metabolism of vinyl chloride is postulated to occur via a secondary pathway involving epoxidation and/or peroxidation. Present data indicate that vinyl chloride is metabolized to an activated carcinogen electrophile (Van Duuren, 1975; Montesano and Bartsch, 1976; Kappus, et al. 1976) and is capable of covalently reacting with nucleophilic groups or cellular macromolecules.

TABLE 1

Percentage of the Administered ^{14}C Activity per Gram of Tissue After Administration of (^{14}C) Vinyl Chloride[a] (Watanabe, et al. 1976a)

Tissue	Dose (mg/kg)		
	0.05	1.0	100
Liver	0.172 ± 0.025[b]	0.182 ± 0.005	0.029 ± 0.002
Skin	0.070 ± 0.023	0.076 ± 0.010	0.010 ± 0.002
Carcass	0.027 ± 0.007	0.046 ± 0.002	0.007 ± 0.001
Plasma	0.041 ± 0.004	0.053 ± 0.007	ND[c]
Muscle	0.028 ± 0.003	0.031 ± 0.003	0.006 ± 0.001
Lung	0.050 ± 0.003	0.061 ± 0.003	0.011 ± 0.001
Fat	0.030 ± 0.004	0.045 ± 0.008	0.006 ± 0.001

[a] Remaining in the body after 72 hr.
[b] Mean ± SE, five rats per dose
[c] Not detectable above background

There is ample evidence that the mixed function oxidase (MFO) system may be involved in the metabolism of vinyl chloride. Pretreatment of rats with phenobarbital, which induces the MFO system, also enhances liver toxicity of vinyl chloride (Jaeger, et al. 1974). Rat liver microsomes catalyze the covalent binding of vinyl chloride metabolites to protein and nucleic acids (Kappus, et al. 1975; 1976); chloroethylene oxide is thought to be the primary microsomal metabolite capable of alkylating these cellular macromolecules (Laib and Bolt, 1977). Hathway (1977) reports *in vitro* depurination of calf thymus DNA by chloroacetaldehyde identical to that observed in hepatocyte DNA following administration of vinyl chloride to rats *in vivo*.

Excretion

Excretion of ^{14}C activity within 72 hours following a single oral dose of ^{14}C-labeled vinyl chloride is shown in Table 2. Administration of vinyl chloride by inhalation produced almost identical results (Watanabe, et al. 1976b). Two or three major metabolites are identified as indicated in Table 3; again, the route of administration has no effect.

Green and Hathway (1975) measured the excretion of 250 µg ^{14}C-vinyl chloride per kg body weight administered to rats by intragastric, intravenous (femoral vein), or intraperitoneal routes. During the first 24 hours after treatment, more than 96 percent was excreted from the animals. The rats given vinyl chloride by the intragastric route exhaled 3.7 percent as vinyl chloride, 12.6 percent as CO_2, 71.5 percent labeled material in the urine, and 2.8 percent in the feces. Intravenous injections resulted in 99 percent exhaled as vinyl chloride, 10.3 percent as CO_2, 41.5 percent of the label excreted in the urine, and 1.6 percent in the feces.

TABLE 2

Percentage of Administered ^{14}C Activity Recovered Following A Single Oral Dose of Vinyl Chloride[a] (Watanabe, et al. 1976a)

	Dose (mg/kg)		
	0.05	1.0	100
Expired:			
As VC	1.43 ± 0.13[b]	2.13 ± 0.22	66.64 ± 0.67
As CO_2	8.96 ± 0.59	13.26 ± 0.47	2.52 ± 0.13
Urine	68.34 ± 0.54	59.30 ± 2.75	10.84 ± 0.95
Feces	2.39 ± 0.52	2.20 ± 0.39	0.47 + 0.06
Carcass and tissues	10.13 ± 1.93	11.10 ± 0.47	1.83 ± 0.14
Cage wash[c]	0	0.84 ± 0.45	0
Total recovery	91.25 ± 2.47	88.83 ± 1.98	82.30 ± 0.43

[a]Percentage of dose excreted over 72 hr. Only the ^{14}C activity associated with the expired VC can be attributed to VC per se.
[b]Mean ± SE five rats per dose.
[c]Distilled water wash of metabolism cage at termination of the study.

TABLE 3

Separation of ^{14}C-containing Urinary Metabolites from Rats Given Vinyl Chloride[a] (Watanabe, et al. 1976a)

	Compound	Dose (mg/kg) 0.05(4)[b]	1.0(5)	100(5)
(A)	N-acetyl-S-(2-hydroxyethyl)-cysteine	30.4 ± 2.0[c]	36.2 + 3.9	29.1 ± 2.0
(B)	Thiodiglycolic acid	25.6 + 1.9	23.7 ± 1.1	25.4 ± 0.9
(C)	Unidentified	38.6 + 2.9	34.5 ± 4.6	36.6 ± 2.0
	Total	94.6	94.4	91.1

[a]Metabolites were separated and quantitated by high pressure liquid chromatography. Values are expressed as percentage of total urinary radioactivity.

[b]( ) = Number of animals per dose

[c]Mean ± SE

EFFECTS

Acute, Subacute, and Chronic Toxicity

Acute toxicity tests with vinyl chloride were carried out by Patty, et al. (1930) of the Bureau of Mines, Department of Commerce. Single exposure of guinea pigs to vinyl chloride gas, 10 percent in air, resulted in narcosis and death within 30 to 60 minutes. Lower concentrations resulted in ataxia and narcosis. Pathological findings at necropsy were congestion and edema of the lungs and hypermia of the kidneys and liver. A number of investigators have made similar observations when examining the acute inhalation toxicity of vinyl chloride in mice, rats, guinea pigs, rabbits, cats, dogs (Peoples and Leake, 1933; Lester, et al. 1963; Mastromatteo, et al. 1961; Haley, 1975; Prodan, et al. 1975). In animal studies, LD50's at 2 hours ranged from 117,500 ppm for mice to 230,800 ppm for rabbits. Deaths of two Canadian workers were reported in 1960 (Danziger, 1960) following acute exposures to vinyl chloride gas. At autopsy, there was congestion of the liver, spleen and kidneys.

The earliest reports of vinyl chloride-associated liver abnormalities were from the USSR (Tribukh, et al. 1949). In 1957 the USSR set upper limits of industrial exposures to vinyl chloride at 400 ppm. As referenced by Marsteller and Lebach (1975), reports from Romania in 1963 and 1967 described vinyl chloride-associated Raynaud's syndrome, dermatitis, scleroderma, thyroid insufficiency, and hepatomegaly. In 1966, Cordier, et al. were the first to describe acroosteolysis of the distal phalanges combined with a Raynaud-like symptomatology. Subsequently, other cases

were reported in the literature. The first cases in the U.S. of occupational vinyl chloride-associated acroosteolysis were reported by Wilson, et al. in 1967. These reports prompted studies of chronic toxicity (Viola, 1970), and to further observations of vinyl chloride-induced neoplasia in rats (Viola, et al. 1971).

Maltoni, in a series of reports starting in 1973, confirmed the carinogenicity of inhaled vinyl chloride in experimental animals and listed several types of neoplasms including angiosarcoma of the liver. Confirmation of observations made in animal models came in 1974 with the report of vinyl chloride-associated angiosarcoma of the liver in vinyl chloride polymerization workers at the B.F. Goodrich plant in Louisville, Kentucky (Creech and Johnson, 1974). By December, 1975, similar reports came from 11 different countries culminating in 64 known cases (according to the latest compilation by Spirtas and Kaminski, 1978).

Synergism and/or Antagonism

Hefner, et al. (1975a) inhibited the metabolism of vinyl chloride by administering to rats 320 mg/kg of pyrazole 1 hour prior to inhalation of the gas. Pyrazole is an inhibitor of alcohol dehydrogenase, xanthine oxidase, and other enzymes (Carter and Isselbachus, 1972). Pretreatment of rats with ethanol (5 mg/kg, 95 percent) also inhibited vinyl chloride metabolism.

A study of the effects of ingested ethanol (5 percent in water ad libitum) on the induction of liver tumors in Sprague-Dawley rats by year-long vinyl chloride inhalation indicates that chronic ingestion of alcohol increases the incidence of liver tumors and tumors in other sites (Radike,

1977b). The first animals treated with 5 percent ethanol and 600 ppm vinyl chloride died of angiosarcoma of the liver in 39 weeks; the first treated with vinyl chloride died due to liver tumor proliferation in 53 weeks.

Jaeger (1975) conducted experiments to determine the interaction between vinylidene chloride (1,1-DCE) and vinyl chloride. In this experiment the effects of 4-hour exposures to 200 ppm of vinylidine chloride and 1,000 ppm vinyl chloride were less than if 1,1-DCE was given alone. Simultaneous 4-hour exposures to 200 ppm vinylidene chloride and 1,000 ppm vinyl chloride indicated that vinyl chloride prevented injury caused in rats by the administration of 1,1-DCE alone. Injury was indicated by an elevation in serum alanine a-ketoglutarate transaminase. These two monomers are used together in the production of vinyl copolymers and exposure to both agents was reported by Kramer and Mutchler (1972).

Teratogenicity

Animal studies using three species (mice, rats, and rabbits) indicate that inhalation of vinyl chloride does not induce gross teratogenic abnormlities in offspring of mothers exposed 7 hours daily to concentrations ranging from 50 to 2,500 ppm (John, et al. 1977); however, excess occurrences of minor skeletal abnormalities were noted. Mice and rats were exposed on days 6 and 15 and rabbits on days 6 to 18 of gestation. At high concentrations there was evidence of increased fetal death in all three species. Radike, et al. (1977a) also did not observe gross abnormalities in the offspring of rats exposed 4 hours daily on the 9th to the 21st day of gestation by inhalation to 600 or 6,000 ppm vinyl chloride; minor skeletal abnormailities did occur in excess.

Mutagenicity

Vinyl chloride is mutagenic in a number of biological systems. The mutagenic action of vinyl chloride appears to be dependent upon its metabolic conversion into chemically reactive metabolites (e.g., chloroethylene oxide, 2-chloroacetaldehyde). The mutagenic effects of vinyl chloride have been demonstrated in: (1) metabolically activated systems using Salmonella typhimurium (Bartsch, et al. 1975; McCann, et al. 1975; Elmore, et al. 1976; Runnag, et al. 1974; Garro, et al. 1976) developed by Ames, et al. (1973) in which the genetic indicator reverts to histidine prototrophy by base-pair substitutions, or by base-pair insertions or deletions; (2) Escherichia coli K12 bioauxotrophic strain with back mutation system arginine^{+} (Greim, et al. 1975); (3) several species of yeast inducing forward mutations and gene conversions at specific loci (Loprieno, et al. 1976, 1977); (4) in germ cells of Drosophila (Verbugt, 1977); (5) and Chinese hamster V79 cells (Huberman, et al. 1975).

The mutagenic activity of inhaled vinyl chloride (3,000, 10,000, or 30,000 ppm for 6 hours a day for 5 days) was assessed in fertile male CD-1 mice with the dominant lethal assay (Anderson, et al. 1976). At these high concentrations vinyl chloride was not mutagenic as judged by scoring of post-implantation fetal deaths, pre-implantation egg losses and reduction in fertility. Positive control tests indicated that the dominant lethal effect was expressed in the CD-1 mice used in these experiments.

In relation to man, several investigators have observed a significantly higher incidence of chromosomal aberrations

in the lymphocytes of workers chronically exposed to high levels of vinyl chloride (Ducatman, et al. 1975; Purchase, et al. 1975; Funes-Cravioto, et al. 1975). Most of the damage involved gross changes such as fragmentations or rearrangements. These studies are more fully discussed in the Human Effects Section.

Carcinogenicity

Inhalation-Animal Studies: Viola, et al. 9197) reported the carcinogenic response of male rats (Ar/IRE Wistar strain) exposed to vinyl chloride by inhalation (Table 4). After the year-long exposure, animals were killed at 20-day intervals. Skin tumors were first noted at approximately 10 months; tumors in the lungs and bones were observed at about 11 months.

TABLE 4

Oncogenic Effects of Inhaled Vinyl Chloride
(Viola, et al. 1971)

Conc. VC (ppm) 4 hrs/day, 5 days/wk 12 months	Number Rats	Skin epidermoid Carcinomas	Lung Adenocarcinomas & Squamous cell Carcinomas	Bones Osteochondroma	Total
30,000	26	17	6	5	25
No treatment	25	-	-	-	-

Caputo, et al. (1974) exposed larger numbers of male and female rats (A and IRE Wistar strain) by inhalation to various concentrations of vinyl chloride. Carcinomas and sarcomas were observed in all groups except those exposed to 50 ppm (Table 5). Tumors appeared between 8 and 13 months from the beginning of the inhalation treatment. These inves-

tigators also exposed rabbits by inhalation to 10,000 ppm vinyl chloride for 15 months (Table 5) and reported incidence of lung and skin carcinomas.

In 1974 and 1975, Maltoni and Lefemine reported a series of experiments concerning the effects of inhalation exposure on rats, mice, and hamsters to vinyl chloride at concentrations ranging from 50 to 10,000 ppm for varying periods of time. Animals were observed for their lifetime. Angiosarcomas in the liver occurred in all three species as well as tumors at several other sites. The following tables summarize some of their findings (Tables 6-10). Male hamsters and male and female rats and mice were used in these experiments. A differential response of the sexes was not reported.

The most recent publication of Maltoni's ongoing experiments (1976) does not report average latent periods or the total number of animals with tumors per treatment group. For this reason, both Maltoni and Lefemine's (1975) and Maltoni's (1976) data are included in the same study at two different times.

Experiments which are not yet completed (Maltoni, 1976) include: (1) inhalation exposure of male and female Sprague-Dawley rats to concentrations of 200, 150, and 100 ppm for 52 weeks (Table 11); (2) inhalation exposure of male and female Sprague-Dawley rats lasting only 17 weeks, observed at last report up to 114 weeks (data not included) (preliminary results indicate that a 17 week exposure produces the same kinds of lesions observed following a 52-week exposure); (3) 52-week exposure of male Wistar rats observed for 88 weeks with preliminary results in general confirming

results with Sprague-Dawley rats; and (4) exposure of newborn rats by inhalation to high concentrations of vinyl chloride for 5 weeks results after 48 weeks indicating that angiosarcomas in the liver and hepatomas have been identified.

TABLE 5

Incidence of Tumors in Rats and Rabbits Exposed to Vinyl Chloride by Inhalation (Caputo, et al. 1974)

Conc. VC (ppm) 4 hrs/day, 5 days/wk 12 months	Number of Animals	Liver Angiosarcomas Cholangiomas	Lung Adeno-Alveolar Carcinomas	Skin Squamous cell Carcinoma Acanthoma	Other
	Rats				
20,000	150	31	21	67	7
10,000	200	16	16	34	8
5,000	200	12	4	20	2
2,000	200	10	8	6	6
500	150	4	-	3	-
50	200	-	-	-	-
No treatment	200	-	-	-	-
15 months	Rabbits				
10,000	40	-	6	12	-
No treatment	20	-	-	-	-

Maltoni (1976) also observed four subcutaneous angiosarcomas, four zymbal gland carcinomas, and one nephroblastoma in 66 offspring of 60 Sprague-Dawley rats exposed by inhalation 4 hrs/day to 10,000 or 6,000 ppm vinyl chloride from the 12th to the 18th day of gestation (21-day gestation). At the time of Maltoni's publication (1976), 20 offspring were living at 115 weeks' post-exposure.

TABLE 6

Incidence of Tumors in Sprague-Dawley Rats Exposed 4 hrs/day, 5 days/wk 52 Weeks By Inhalation to Various Concentrations of Vinyl Chloride: Results After 135 Weeks (Maltoni and Lefemine, 1975)

Conc. VC (ppm)	Number of Animals		Liver		Kidney		Zymbal Gland			
	Total	Corrected	Angio sarcomas	Average Latency (wk)	Nephro blastomas	Average Latency (wk)	Carcinomas	Average Latency (wk)	Other	Total Number of Rats with one or more tumors
10,000	69	61	9	64	5	59	16	50	25	38
6,000	72	60	13	70	4	65	7	62	19	31
2,500	74	59	13	78	6	74	2	33	18	32
500	67	59	7	81	4	83	4	79	11	22
250	67	59	4	79	6	80	-	-	9	16
50	64	59	1	135	1	135	-	-	12	10
No treatment	68	58	-	-	-	-	-	-	10	6

TABLE 7

Incidence of tumors in Swiss Mice Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk, 30 weeks: Results After 41 Weeks (Maltoni and Lefemine, 1975)

Conc VC (ppm)	Number of Animals		Liver Angiosarcomas	Pulmonary Tumors		Mammary Carcinomas		Other	Total Number of Mice One or More Tumors
	Total	Corrected		No.	Average (wks)	No.	Average (wks)		
10,000	60	50	4	27	34	9	28	9	28
6,000	60	54	2	22	33	8	33	5	27
2,500	60	53	4	12	35	4	32	3	13
500	60	58	4	16	34	2	33	2	17
250	60	58	3	11	34	6	30	1	15
50	60	57	-	-	-	7	35	4	8
No treatment	150	141	-	1	39	-	-	-	1

TABLE 8

Incidence of Tumors in Swiss Mice Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk, 30 weeks: Results After 81 Weeks (Maltoni, 1976)

Conc. VC (ppm)	Number of Animals		Number of Animals with Tumors		
	0	♀	Liver Angiosarcomas	Pulmonary Tumors	Other
10,000		60	8	35	26
6,000		60	5	38	24
2,500		60	11	30	25
500		60	11	38	26
250		60	11	33	35
50		60	1	2	25
No treatment		150	-	8	1

TABLE 9

Incidence of Tumors in Golden Hamsters Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk For 30 Weeks: Results After 48 Weeks (Maltoni and Lefemine, 1975)

Conc VC (ppm)	Number of Animals		Liver Angiosarcomas	Other	Total Number of Animals with one or more Tumors
	Total	Survivors			
10,000	35	19	-	3	3
6,000	32	21	-	8	5
2,500	33	19	-	5	4
500	33	23	1*	4	4
250	32	18	-	2	2
50	33	23	-	5	5
No treatment	70	49	-	2	2

*More than 18 weeks post-exposure

TABLE 10

Incidence of Tumors in Golden Hamsters Inhaling Vinyl Chloride 4 hrs/day, 5 days/wk, for 30 Weeks: Results After 76 Weeks (Maltoni, 1976)

Conc. VC (ppm)	Number of Animals		Liver Tumors Angiosarcoma Angiomas Hepatomas	Other
	Total	Survivors		
10,000	35	1	-	13
6,000	32	3	3	10
2,500	33	4	4	10
500	33	4	2[a]	8
250	32	4	-	4
50	33	5	-	10
No treatment	70	14	-	4

[a]Angiosarcomas

TABLE 11

Incidence of Tumors in Sprague-Dawley Rats Exposed 4 hrs/day, 5 days/week, 52 Weeks by Inhalation to Vinyl Chloride: Results After 89 Weeks (Maltoni, 1976)

Conc. VC (ppm)	Number of Animals		Liver		Zymbal gland carcinomas	Angiosarcomas Other Sites
	Total	Survivors	Angiosarcoma	Nephroblastomas		
200	120	41	7	2	-	1
150	120	45	3	4	-	1
100	120	49	1	8	1	-
No treatment	185	76	-	-	1	1

Recent inhalation studies with albino CD-1 mice and CD rats (Charles River Breeding Lab) confirm the carcinogenicity of vinyl chloride (Lee, et al. 1977). This study was designed to define biochemical changes relating to histological and neoplastic lesions. For each species 360 animals were divided into five groups, each consisting of 36 males and 36 females. Each group of both species was exposed to 50, 250, or 1,000 ppm vinyl chloride or 55 ppm vinylidene chloride 6 hr/day, 5 days/wk. Four animals of each species, sex, and exposure level were terminated at the end of 1, 2, 3, 6, and 9 months and the surviving animals terminated at 12 months. After 12 months, bronchioalveolar adenomas, mammary gland tumors, and angiosarcomas in the liver and other sites developed in mice exposed by inhalation to 50, 250, or 1,000 ppm vinyl chloride. Rats exposed to 250 or 1,000 ppm vinyl chloride developed angiosarcoma in the liver, lungs, and other sites (Lee, et al. 1978).

There is evidence that ingested alcohol promotes the effects of inhaled vinyl chloride (Radike, et al. 1977b). Three hundred and twenty male Sprague-Dawley rats were divided into four groups; two groups received 5 percent ethanol in water 4 weeks prior to vinyl chloride inhalation (600 ppm 4 hrs/day, 5 days/wk, 12 months). After 60 weeks, timed from the first exposure to vinyl chloride, the first death from liver angiosarcoma in rats exposed to vinyl chloride was at 53 weeks; in rats ingesting 5 percent ethanol and inhaling vinyl chloride the first death from angiosarcoma in the liver was at 39 weeks. Cancerous lesions were identified in only 13 rats (Table 12).

Maltoni (1976) exposed male Sprague-Dawley rats by ingestion (stomach tube) to vinyl chloride in olive oil, once daily, 4 to 5 days/week, for 52 weeks. Results after 52 weeks are reported in Table 13. In addition, studies are now in progress to determine the incidence and type of cancer produced by ingestion of low doses of vinyl chloride, i.e., 1.0, 0.3, and 0.03 mg/kg/day (Maltoni, 1976).

The primary effect associated with vinyl chloride exposure in man is an increased risk of cancer in several organ systems including angiosarcoma of the liver. Liver angiosarcoma is an extremely rare liver cancer in humans with 26 cases reported annually in the U.S. (Natl. Cancer Inst. 1975). Human data of carcinogenic effects of vinyl chloride have been obtained primarily from cases of occupational exposures of workers. The latent period has been estimated to be 15 to 20 years following onset of exposure; however, recent case reports indicate a longer average latent period (Spirtas and Kaminski, 1978).

Epidemiological studies of vinyl chloride exposed workers have primarily focused on cases of angiosarcoma of the liver. The basis for this emphasis is clear; a primary problem in all epidemiological investigations is the establishment of a cause/effect relationship between a harmful agent and a population under study. Hemangiosarcoma of the liver is a type of cancer rarely occurring in the general population. Because of this rare occurrence of hemangiosarcoma in man, it is much easier to draw a casual relationship between exposure to vinyl chloride and the development of this tumor. The linking of vinyl chloride to other types of cancers through epidemiological evidence is more tenuous.

TABLE 12

Tumors in 13 Rats Exposed to Vinyl Chloride or to 5 Percent Ethanol and Vinyl Chloride (Radike, et al. 1977b)

Group Treatment	Number of Animals	Liver		Lung	Kidney
		Angio-sarcoma	Hepatocellular-carcinoma	Angiosarcoma	Angiosarcoma Fibrosarcoma
600 ppm VC[a]	6	2	1	-	-
600 ppm VC[a] 5% Ethanol	7	5	2	1	1 (each)

[a]4 hrs/day, 5 days/wk

TABLE 13

Incidence of Tumors in Sprague-Dawley Rats Ingesting Vinyl Chloride in Olive Oil: Results After 55 Weeks (Maltoni, 1976)

Conc. VC (mg/kg)	Number of Animals		Liver Angiosarcomas	Angiosarcomas Other Sites
	Total	Survivors		
50.00	80	57	1	1
16.65	80	66	1	-
3.33	80	62	-	-
Olive Oil Alone	80	68	-	-

The work of Maltoni, et al. (1974) among others was of primary importance in focusing attention on the potential for liver angiosarcoma in workers exposed to vinyl chloride. He demonstrated liver angiosarcoma as a specific lesion in rats following vinyl chloride inhalation exposures. Subsequently, the first four cases of liver angiosarcoma in vinyl chloride exposed workers were reported (Creech and Johnson, 1974).

Tabershaw/Cooper Associates (1974) conducted a mortality study of vinyl chloride workers. Mortality calculations included only those workers which could be traced in the followup study, i.e., 7,129 of 8,384 workers. These individuals were from 33 different plants and all had been exposed to vinyl chloride for at least 1 year. The mean employment duration for the group of workers under study was 80 months (in contrast to 44 months for those not located), but the traced workers entered employment about 10 years later. Among the 7,128 workers which were located there were 854 with exposures of 20 years or longer and 1,640 exposed 15 or more years.

Compared to the general male U.S. population the overall mortality rate was found to be lower i.e., 75 percent that of expected rate. Specific causes of death was no greater than expected and no deaths seemed attributable to angiosarcoma. Standardized mortality ratios (SMR) for malignant neoplasms in general increased with increasing exposure level and/or duration. In the group identified as the high exposure group there were increases in liver cancer (primarily angiosarcoma), respiratory system cancers, and brain cancers. These differences were not statistically

significant. (Tabershaw/Cooper Assoc. Inc. 1974; Tabershaw and Gaffey, 1977).

Dow Chemical Co. (Holder, 1974) conducted a mortality study of 594 workers in a single plant exposed to vinyl chloride between 1942 and 1960. Workers were assigned to exposure groups based on the highest level of exposure for at least 1 month (low group - time-weighted average less than 25 ppm vinyl chloride, intermediate-time-weighted average 25 to 200 ppm; high-time-weighted average 200 to 300 ppm). Also included in the high group were workers from the intermediate group frequently exposed to 1,000 ppm for short time periods.

Total mortality was 91 percent of expected among the vinyl chloride exposed workers. No deaths due to liver cancer were reported and only a total of 13 cases of neoplasms were reported as opposed to 15.4 expected. However, nine of these malignancies occurred in the high exposure group as compared to 5.1 expected (due to small number of deaths, this difference was not tested for significance). Eight of these malignancies were in workers with 15 or more years of exposure.

Monson, et al. (1974) conducted a proportional mortality study of workers from two vinyl chloride plants who died from 1947-1973. Death certificates were obtained for 142 out of 161 workers who died within this time period. Deaths attributable to cancer were 50 percent higher than expected (a statistically significant difference). A 900 percent increase in cancers of the liver and biliary tract was noted (five angiosarcomas). Excluding angiosarcoma, a 275 percent excess was observed in the remaining forms

of cancer. Two brain tumors (320 percent excess) and 13 lung cancers (60 percent excess) were observed. In addition the cancer death rate increased during the period.

Nicholson, et al. (1975) studied a group of 257 workers (of whom 255 were traced) exposed to vinyl chloride for at least 5 years prior to 1946. Their mortality status was evaluated beginning 10 years after start of employment until 1974. Exposures were estimated to often exceed 10,000 ppm. Among the 24 deaths were three cases of angiosarcoma of the liver. Preliminary findings indicated a 25 percent increase over expected in all deaths and a 131 percent increase in all cancer deaths although neither of these increases was statistically significant.

The National Institute for Occupational Safety and Health (NIOSH) conducted a study which involved 950 individuals who were exposed for at least 5 years and for whom at least 10 years had elapsed since initial employment. Of these individuals, 285 were located. A total of 109 deaths was reported versus 105 expected (not a significant difference). A 57 percent increase over the expected for cancer deaths was noted - statistically significant factor. Cancerous lesions were noted in the respiratory system, blood forming tissues, brain, and central nervous system. Liver cancer deaths were twelvefold greater than expected and brain cancer deaths were fivefold higher (both statistically significant differences). (Wagoner, 1974).

Ott, et al. (1975) have reexamined much of the mortality data reported by Tabershaw and Gaffey (1974) and have included more clearly defined exposure levels and followup of former company employees. The basic findings remain

unchanged: no increase over expected in malignant neoplasms was found in the low exposure group (time-weighted average from 10 to 100 ppm) and an increase in deaths due to malignant neoplasms was observed in the high exposure group (time-weighted average was greater than 200 ppm).

Chiazze, et al. (1977) have reported a cross-sectional mortality study of 4,341 employees from 17 PVC plants who died between 1964 and 1973. No angiosarcoma deaths were identified. Total cancer deaths increased in white employees (especially due to cancer of the digestive system). In white women employees deaths from cancer of the breast and urinary organs were greater than expected.

On the other hand, in a mortality study of 7,000 British workers exposed to vinyl chloride between 1940 and 1974, the authors found no evidence of increased cancer mortality other than from liver cancer. In this study, four cases of malignant liver tumor were diagnosed and two of these were confirmed to be angiosarcoma. Both cases were in men exposed to high levels of vinyl chloride (Fox and Collier, 1977).

In addition, Byren, et al. (1976) traced 21 of 771 Swedish vinyl chloride plant workers. A four-to fivefold increase over expected in pancreas and liver tumors was found and two cases were diagnosed as angiosarcoma. Numbers of other tumors did not deviate significantly from expected.

Ten cases of hepatic angiosarcoma have been found among the relatively small work force employed at a vinyl chloride polymerization plant in Quebec, this being the largest number of cases to be diagnosed in a single plant (Makk, et al. 1976). As a result of this unusually large number of occurrences, Delorme and Theriault (1978) have retrieved

more detailed information on these employees. The authors suggest that the cases of hepatic angiosarcoma appear to be associated with high vinyl chloride exposure levels and overtime work hours. No correlation was found between occurrence of this tumor and alcohol or cigarettes.

In the workers engaged in the polymerization of vinyl chloride who were studied (Popper and Thomas, 1975), the characteristic hepatic fibrosis was present in all cases of angiosarcoma. Although the relation of fibrotic lesions to the development of angiosarcomas requires further study, a transition from the fibrotic stage to angiosarcoma is suggested by the focal proliferation of the sinusoidal lining cells and of the hepatocytes that are seen in the fibrotic stage but become even more pronounced in the initial stages of angiosarcoma development. These findings suggest that the fibrotic lesions without angiosarcomas, frequently described in the workers exposed to vinyl chloride (Lilis, et al. 1975), might be only the pre-stage of developing neoplastic lesions. The diagnosis of the fibrotic lesions in these workers may imply a longer latency period for tumor initiation based on a possibly lower exposure level. The series of changes observed in the liver appear to represent a multicentric development of angiosarcoma and are similar to the changes induced by thorotrast and inorganic arsenicals (Berk, et al. 1976).

In the most recent update of the NIOSH register (Spritas and Kaminski, 1978) a total of 64 cases of hepatic angiosarcoma has been identified worldwide among vinyl chloride-exposed industrial workers. A listing of all documented cases by country is presented in Table 14.

Of the 64, 23 cases have been reported in the U.S., representing more than one third of all diagnosed cases. Six of these cases have been documented since 1975.

It is apparent from Table 14 that both the age at diagnosis and the latency period for cancer induction appear to be increasing. The authors suggest three explanations for this phenomena: (1) early cases may have had heavier exposure; (2) the initial cases were more biologically susceptible; (3) random fluctuation. Should the first of these hypotheses prove to be correct, it would have a profound impact upon risk assessment related to low level exposures of vinyl chloride in the next 10 to 20 years.

In addition to the large numbers of workers occupationally exposed to vinyl chloride, individuals residing near PVC processing plants may also be at risk (Baxter, et al. 1977). It has been estimated that 4.6 million people live within 5 miles of PVC or vinyl chloride production plants in the United States. Prior to restriction of plant emissions the average exposure level for this population has been estimated to be 17 ppm (Kuzmak and McGaughy, 1975).

Brady, et al. (1977) have examined annual rates of hepatic angiosarcoma from 1970 through 1975 in residents of the State of New York (excluding New York City). Exposures to arsenic, vinyl chloride, or thorium dioxide were found to be significant factors in the etiology of these tumors. Direct exposures to these agents could not be demonstrated for 19 of the 26 study cases. Five of the 19 patients lived closer to vinyl chloride plants than did their matched controls. This may lend some support to the idea that "indirect modes of exposure, not specifically related to occupation might be important in the etiology of this disorder" (Brady, et al. 1977).

TABLE 14

Angiosarcoma of the Liver in Vinyl Chloride/PVC Workers
(Spirtas and Kaminski, 1978)

Country	Case No.	Birth Date	1st VC of PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from 1st Exposure to Diagnosis	Total Years of Exposure	Date of Death
Belgium	01	00-00-00	00-00-00	00-00-00	00	00	00	06-29-76
Canada	01*	12-15-13	00-00-44	00-00-55	41	11	11	09-02-55
Canada	02*	03-06-14	00-00-43	00-00-57	43	14	14	12-21-57
Canada	03*	08-26-19	00-00-41	00-00-62	42	21	20	03-22-62
Canada	04*	04-05-19	00-00-45	00-00-67	48	22	22	01-21-68
Canada	05*	05-07-11	00-00-44	00-00-68	57	24	05	07-05-68
Canada	06*	12-15-19	00-00-47	00-00-71	51	24	23	04-10-71
Canada	07*	11-09-19	00-00-46	00-00-72	53	26	25	12-24-72
Canada	08	05-13-20	00-00-61	00-00-73	53	12	05	06-12-73
Canada	09	07-19-21	00-00-46	00-00-74	53	28	26	09-04-74
Canada	10	05-16-15	00-00-53	00-00-76	61	23	14	04-00-77
Czechoslovakia	01*	00-00-28	00-00-57	00-00-73	46	16	16	00-00-74
Czechoslovakia	02*	00-00-26	00-00-51	00-00-66	40	15	15	00-00-66
Fed Rep Germany	01*	06-04-30	10-01-56	09-19-68	38	12	12	01-25-69
Fed Rep Germany	02*	07-26-31	10-14-57	09-25-70	39	13	12	12-14-71
Fed Rep Germany	04	09-04-30	04-16-57	00-00-74	44	17	17	11-25-74
Fed Rep Germany	05*	01-01-32	12-16-62	00-00-75	43	13	12	01-09-75
Fed Rep Germany	07*	09-29-26	04-15-54	00-00-75	49	21	12	11-13-75
Fed Rep Germany	08*	10-19-17	04-19-54	00-00-75	58	22	21	12-25-75
Fed Rep Germany	09*	12-13-34	12-02-59	06-16-76	42	17	15	Alive
Fed Rep Germany	10*	07-25-29	10-10-55	06-28-77	47	22	22	06-28-77
Fed Rep Germany	11*	12-29-36	01-02-61	00-00-77	41	16	10	03-07-77
France	01*	04-15-24	01-00-46	02-18-67	43	21	19	02-19-67
France	02	06-03-11	07-06-59	01-08-75	63	15	12	01-24-75
France	03*	00-00-19	00-00-46	01-00-75	55	29	29	06-29-75
France	04*	01-27-27	10-19-49	01-04-76	49	26	26	01-04-76
France	05*	01-29-38	00-00-65	04-00-76	38	11	10	05-13-76
France	06*	04-14-34	00-00-58	09-00-76	42	18	17	09-12-76
France	07	00-00-27	07-01-50	07-00-76	49	26	23	07-02-76
France	08*	04-01-34	05-23-57	12-03-76	42	19	19	01-30-77
Great Britain	01*	04-20-01	00-00-44	12-00-72	71	28	22	12-00-72
Great Britain	03	06-02-37	02-00-66	12-00-74	37	09	04	12-24-74

TABLE 14

Angiosarcoma of the Liver in Vinyl Chloride/PVC Workers
(Spirtas and Kaminski, 1978)

Country	Case No.	Birth Date	1st VC of PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from 1st Exposure to Diagnosis	Total Years of Exposure	Date of Death
Italy	02*	11-13-29	00-00-57	12-13-72	43	15	06	12-00-72
Italy	03*	03-14-20	00-00-53	07-10-75	55	22	21	07-10-75
Japan	01	08-01-22	04-00-53	08-21-74	52	22	22	10-24-75
Norway	01*	12-23-15	03-00-50	12-20-71	56	22	21	01-04-72
Sweden	01*	06-23-27	08-14-51	08-00-74	43	19	18	10-20-70
Sweden	03*	06-10-10	05-00-47	03-19-76	65	29	21	03-19-76
Sweden	04*	11-16-14	00-00-46	05-12-77	62	31	31	05-12-77
U.S.A.	01*	10-17-23	12-09-48	03-03-73	49	24	21	03-03-73
U.S.A.	02*	08-19-33	11-15-55	05-00-70	37	14	13	09-28-71
U.S.A.	03*	05-25-15	11-28-45	12-19-73	58	28	28	12-19-73
U.S.A.	04*	01-15-24	07-06-52	08-19-67	43	15	15	01-07-68
U.S.A.	05*	01-25-12	06-19-44	04-09-64	52	20	20	04-09-64
U.S.A.	06*	11-23-28	01-17-62	02-00-74	46	12	12	07-24-75
U.S.A.	07*	05-03-22	08-27-44	00-00-68	45	24	17	03-23-68
U.S.A.	08*	05-06-20	10-07-46	08-00-61	41	15	15	08-29-61
U.S.A.	09*	11-08-31	05-28-45	03-01-74	43	29	24	03-00-75
U.S.A.	10*	08-16-13	06-12-51	05-00-68	55	17	17	05-10-68
U.S.A.	11*	05-27-09	10-14-46	03-00-70	61	23	23	03-16-70
U.S.A.	12*	11-17-18	09-13-49	05-02-69	50	20	19	05-02-69
U.S.A.	13*	12-01-21	12-11-42	05-00-74	52	32	26	07-04-74
U.S.A.	16*	11-04-27	05-08-50	00-00-69	41	19	04	03-27-69
U.S.A.	17*	05-06-31	06-23-55	10-11-74	43	19	19	Alive
U.S.A.	18*	04-22-28	09-15-54	00-00-75	46	21	11	11-02-75
U.S.A.	19*	00-00-15	00-00-43	06-19-75	60	32	22	04-06-76
U.S.A.	20*	08-31-17	00-00-55	01-30-76	58	21	18	01-30-77
U.S.A.	21*	09-02-09	12-00-46	00-00-77	67	30	21	01-02-77
U.S.A.	22*	10-02-23	07-11-47	01-00-76	52	29	28	12-04-76
U.S.A.	23*	00-00-23	09-00-58	04-06-73	50	15	14	04-06-73
U.S.A.	24*	05-07-17	00-00-39	05-27-77	60	38	26	05-27-77
U.S.A.	25*	08-07-10	02-00-47	03-10-77	67	30	20	03-10-77
Yugoslavia	01*	04-05-14	00-00-53	04-08-73	59	20	20	04-08-73
Yugoslavia	02*	11-15-31	00-00-50	07-12-73	42	23	18	07-12-73
Total Reported Cases	64							

*Diagnosis was microscopically confirmed
00 indicates unknown data

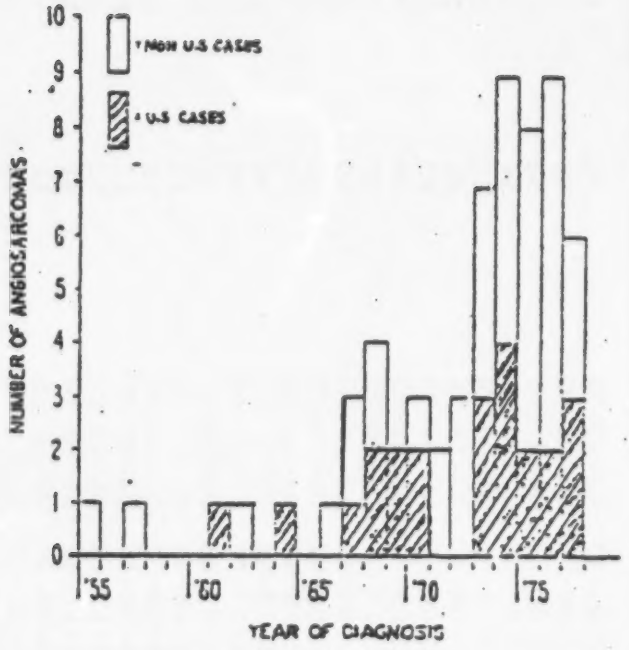

Figure 1

Number of cases of vinyl chloride/PVC related angiosarcomas reported to NIOSH by year of diagnosis (representing only 63 of the 64 cases known to NIOSH since information on diagnosis is missing for one case) (Spirtas and Kaminski, 1978)

It should be noted that a relatively short time period elapsed since the large scale development of the vinyl chloride-PVC industries. If the trend of increased age at diagnosis and the longer latent period for hepatic angiosarcoma induction are indeed related to lower levels of occupational exposure, then the latent period for cancer induction as a result of these very low levels of environmental exposure may be much longer than previously anticipated, i.e., it would be many years before the ultimate outcome of these exposures will be known.

Picciano, et al. (1977) have reported no statistically significant differences in chromatid and chromosome aberrations or proportion of abnormal cells in a group of 209 vinyl chloride-exposed workers. These workers were exposed for periods ranging from 1 to 332 months ($\bar{x}$ = 48.5 mo.) to time-weighted average levels of vinyl chloride ranging from 0.3 to 15.2 ppm. Killian, et al. (1975) have also reported a lack of evidence for excess chromosome breakage in a population of vinyl chloride-exposed workers.

On the other hand, Ducatman, et al. (1975) and Purchase, et al. (1975) have reported increased incidence of chromosomal breakage among their cohorts of vinyl chloride-exposed workers populations.

Heath, et al. (1977) examined cytogenetic effects in three groups of industrial workers: PVC polymerization workers (presumed high exposure), PVC processing workers (presumed low exposure) and rubber and tire manufacture workers (presumed negligible exposure). Chromosome breakage in all three groups was significantly greater than in non-industrial controls and overall breakage levels were similar

in all three groups. These data suggest that other agents in addition to vinyl chloride may cause cytogenetic damage in workers employed in similar occupations.

Waxweiler, et al. (1977) reported cytogenetic studies of vinyl chloride workers, plastics workers, and rubber workers. Vinyl chloride workers had a slightly higher rate of chromosome breakage than rubber workers and the plastics workers showed the highest rates of breakage. None of the differences between the industrial groups studied was significant; however, all of the industrial groups had higher chromosome breakage rates than non-industrial controls. Additionally, a significant increase in fetal loss rate was found in wives of workers relative to their husbands' exposure to vinyl chloride.

As to the teratogenic effects, human females are generally not exposed to high concentrations of vinyl chloride; the question arises whether low environmental levels may cause congenital malformations. There are reports of high rates of congenital defects in three small communities in which vinyl chloride polymerization plants are located. Significantly greater numbers of malformations of the central nervous system, upper alimentary tract, genital organs, and club foot were reported (Infante, 1976; Infante, et al. 1976; Edmonds, et al. 1975). Results of these studies are not completely unequivocal and further studies are needed. Overall, the evidence suggests that exposure of pregnant women to vinyl chloride at significant levels should be avoided.

Exposure of workers to high concentrations of vinyl chloride produces conditions of euphoria and intoxication.

Irritation of the respiratory tract is followed by chronic bronchitis and workers complained of headache, irritability, poor memory, tingling, and weight loss (Suciu, et al. 1975).

There are numerous clinical indications that chronic exposure to vinyl chloride is toxic to humans. Tribukh, et al. (1949) reported hepatitis-like liver changes. Angioneurosis of a spastic character was reported by Filatova, et al. in 1958. Raynaud's syndrome, scleroderma-like skin changes, lytic lesions of the terminal phalanges in hands and feet, and pseudoclubbing of the fingers have been reported in many workers in the U.S. and Europe. This latter condition has been termed occupational acroosteolysis. Cases of this new occupational disease have been reported from around the world (Wilson, et al. 1967; Dinman, et al. 1971; Wedrychowiez, 1976; Harris and Adams, 1967).

Examination by wide-field capillary microscopy of the hands of PVC workers demonstrated capillary abnormalities in a high percentage of exposed men. This non-invasive technique may be useful as a mass-screening procedure in the early detection and prevention of vinyl chloride-associated diseases (Maricq, et al. 1976).

Other long-term effects include functional disturbances of the central nervous sytem with adrenergic sensory polyneuritis (Smirnova and Granik, 1970); thrombocytopenia, splenomegaly, liver malfunction with marked fibrosis in the portal areas, and pulmonary insufficiency with restrictive changes in the lungs (Lange, et al. 1974).

In 1972, Kramer and Mutchler studied workers exposed to vinyl chloride and correlated clinical parameters with environmental exposure. Ninety-eight workers were studied

who had been exposed to vinyl chloride up to 25 years. Tests indicated there were slight changes in physiologic and clinical laboratory parameters suggesting some impairment of liver function.

Increased urinary excretion of monochloroacetic acid has been correlated with an increase in the concentration of inhaled vinyl chloride (Grigorescu and Tiba, 1966). One-year exposure to vinyl chloride caused a decrease in blood catalase activity and an increase in peroxidase, indophenoloxidase, and glutathione (Gabor, et al. 1964).

In humans exposed to vinyl chloride, serum levels of gamma-glutamic transpeptidase (GGTP) appear to be the best clinical parameter for detecting liver abnormalities and reflecting the extent of liver lesions by the degree of elevation. Alkaline phosphatase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, lactic dehydrogenase, and bilirubin levels were also increased in many cases. Location of the liver lesions affected the elevation of specific enzymes found in the plasma. (Makk, et al. 1976).

Ward, et al. (1976) provided data which suggest that vinyl chloride disease is an immune complex disorder. Immunological and immuno-chemical investigations of workers with the syndrome showed the presence of circulating immune complexes in 19 of 28 patients. Abnormalities were also detected in some workers exposed to vinyl chloride who had few or no overt clinical signs. Studies are in progress to investigate all the exposed workers in one factory and also workers in other related industrial plants.

Existing Guidelines and Standards

In the 1950's an upper limit of 500 ppm of VC at the work place was recommended in the United States; for comparison, in the USSR, the upper limit was set at 400 ppm. Exposures in the USA were mostly below the time-weighted average (TWA) of 500 ppm; however, peak exposures as high as 4,000 ppm were recorded in some work areas (Ott, et al. 1975). About 1960, Dow Chemical Company established a company standard for a limit of 50 ppm (TWA). They were successful in reducing exposures to workers to about 25 ppm vinyl chloride, however, excursions up to 500 ppm did occur. Dow Chemical also initiated continuous sampling and analysis using a multi-point remote sampler and gas chromatography.

In 1962, a Threshold Limit Value (TLV) of 500 ppm was set by the American Conference of Government Industrial Hygienists which was later adopted after its establishment by the Occupational Safety and Health Administration (Table 15).

Inhalation exposures dropped drastically after the carcinogenicity of vinyl chloride was reported (Viola, 1971; Maltoni and Lefemine, 1974a; and Creech and Johnson, 1974). The Occupational Safety and Health Administration set an emergency temporary standard of 50 ppm (TWA) on April 5, 1974. A flurry of epidemiological studies was performed. Based on all of the information available at the time, a permanent standard of 1 ppm (TWA) with a maximum excursion of 5 ppm for a period of no longer than 15 minutes in 1 day was promulgated for the workplace (39, FR 35890 (Oct. 4, 1974)). The U.S. EPA and other

TABLE 15

Regulations Concerning Vinyl Chloride (Compiled by J.F. Stara)

Year	Agency or Organization	Air Standard (ppm)	Other Action
1962	ACGIH*	500 (TLV)	
1971	OSHA**	500 (TLV)	
1974 (4/5)	OSHA	50 (Max. TLV)	Emergency temp. standard
1974	EPA***	--	Banned as propellant in pesticide aerosols
1974	FDA+	--	Banned as propellant in cosmetics and drug aerosols
1974	CPSC++	--	Banned as propellent in all aerosols for household use
1974 (10/4)	OSHA	1 (8 hr TWA)	5 ppm max. for 15 min.
1974	U.S. Coast Guard	--	Amended carriage on tank vessels
1975	EPA	--	Declared a hazardous pollutant (under Sec. 112, Clean Air Act), and proposed fugitive emission standard at the outlet not to exceed 10 ppm (acc. to BAT)
1976	EPA	--	Clarified proposed emission standard for various industrial processes including discharges in waste water.

* American Conference of Governmental Industrial Hygienists
** Occupational Safety and Health Administration
*** U.S. Environmental Protection Agency
+ Food and Drug Administration
++ Consumer Product Safety Commission

government agencies (Food Drug Admin., Consum. Prod. Safety Comm.) have begun to investigate vinyl chloride inhalation exposures of humans in the general environment. Because of reports that 41 pesticide spray products contained vinyl chloride as a propellant, there was published (39 FR 14753 (April 26, 1974)), a notice of intent to cancel registrations of all such products. Other aerosol products such as hair spray, also found to utilize vinyl chloride as a propellant, were banned from the market in the U.S. and some other countries shortly thereafter (Int. Agency Res. Cancer, 1974). In 1975, U.S. EPA declared vinyl chloride to be a hazardous substance under Sec. 112 of the Clean Air Act. Further, it proposed in 1975 and 1976 emission standards of total emissions with a limit of 10 ppm at the stack. Other government agencies have published new control measures during this time, or have new standards under consideration, e.g., FDA concerning packaging of food substances containing oil in PVC containers. Since 1975, when EPA published its intent to issue new standards for total emissions at the stack, the proposal was litigated in court action initiated by the Environmental Defense Fund and questioned by industry.

In support of the proposed regulations, the U.S. EPA evaluated the risk to populations living in the vicinity of vinyl chloride and PVC plants in a document entitled "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride" by Kuzmack and McGaughy in 1975. A number of factors influenced the estimate of risk to this population, i.e., the number of persons living at distances up to 5 miles from vinyl chloride and PVC plants, published by the American Public Health Association in 1975 (Table 16).

TABLE 16

Estimate of Exposed Population in the Vicinity of Vinyl Chloride and PVC Plants (Am. Pub. Health Assoc. 1975)

Distance (mi)	Population
0-1/2	47,000
1/2-1	203,000
1-3	1,491,000
3-5	2,838,000
Total	4,579,000

The average exposure of a person chosen at random living in the 5-mile radius was calculated to be 17 ppb.

The total number of persons at risk was estimated at 4.6 million. Using standard diffusion models, the annual average ambient concentrations of vinyl chloride were calculated for distances 0 - 0.5; 0.5 - 1.0; 1.0 - 3.0; and 3.0 - 5.0 miles from the plants (Table 17).

TABLE 17

Annual Average Concentrations (ppb) of Vinyl Chloride in the Vicinity of a Vinyl Chloride and PVC Plant (Kuzmack and McGaughy, 1975)

Distance (mi)	Vinyl Chloride Concentration (ppb)	
	PVC Plant	VC Plant
0-1/2	323	113
1/2-1	57	20
1-3	15	5.2
3-5	5.7	2.0

Quantitative estimates of potential health effects which may result from this exposure level were performed using animal data which were fitted by two different models, i.e., the "linear" and "probit" models.

Data published by Maltoni and Lefemine in 1975 which reported liver hemangiosarcoma induction in rats due to vinyl chloride inhalation, were used for calculation of the probability of angiosarcoma cases in highly-exposed populations of workers. This prediction was tested using epidemiological studies of workers and projecting the results to ambient air concentrations of vinyl chloride in the vicinity of the plants. Incidence rates of hemangiosarcoma in rats were compared to incidence rates in exposed workers with the assumption that a long-term exposure of rats would produce the same incidence of effects as a long-term exposure of humans. In this instance, the incidence rate following 1-year exposure of rats would compare to the incidence rate of 30 years of human exposure.

In treatment of experimental animal dose-response data, two mathematical models are quoted most often in literature reports: The "linear" or "one-hit" model and the "log-probit" model which is closely related to the Mantel-Bryan proposed data treatment (Kuzmack and McGaughy, 1975).

The "linear" model assumes that there is no threshold effect level, i.e., it represents a straight line extrapolation to "zero" level. It is called also a "one-hit" model under the assumption that each small increase of an exposure to a carcinogen has identical probability to cause cancer, notwithstanding the dose level. This model has been widely used in the radiation carcinogenesis evaluation process. In mathematical evaluation of carcinogenic risk due to chemical substances, it is thought that it represents the most sensitive probability, i.e., the upper limit to low dose-related carcinogenic effect because of the detoxifying mech-

anisms of the body. Yet, it provides the mathematical analysis of effect data which appears to be the most prudent to use in extrapolating from high dose level animal data to the rather minute quantities of chemicals found in the environment.

The "log-probit" model analysis of biological data results in a straight line when the logarithms of the dose are plotted against responses - in this case animals with liver angiosarcoma - expressed in probits (probability units). The assumption here is that the observed effects corresponding to dose are related to the variations in susceptibility of the subjects which are assumed to have a log-normal distribution with dose.

Maltoni's liver angiosarcoma data (Experiment BT-1) were analyzed using a linear-dose response model to calculate the probability of incidence of liver angiosarcoma in high level exposed workers during each year of continuous exposure to vinyl chloride. Such treatment of the data resulted in an estimate of 71 cases per year of uninterrupted exposure to 1 ppm of vinyl chloride per million persons exposed. Using the same technique, the probability of cancer in all body organs was approximately doubled, i.e., 150 cases per year of continuous exposure to 1 ppm of vinyl chloride per million persons (Kuzmack and McGaughy, 1978).

Four epidemiological studies in workers (Ott, et al. 1975; Tabershaw and Gaffey, 1974; Nicholson, et al. 1975; Heath and Falk, 1975) were used to estimate the hemangiosarcoma incidence rate based on human experience, and to compare the results with the incidence rates derived from animal data. From the epidemiological data the probability

that a vinyl chloride worker would suffer from angiosarcoma of the liver at some point in his life was calculated to be 0.0031 per year of exposure. If the animal derived-data are converted to a standard work exposure time (7 hrs, 5 days/wk, an exposure to 350 ppm of vinyl chloride), the probability was calculated to be 0.0052. Since such estimates contain a number of inherent errors, the authors concluded that "the slope of the linear animal dose-response relationship for angiosarcomas is consistent with human data".

The results of this analysis were used in estimating the risk to the 4.6 million persons living in the vicinity of the vinyl chloride and PVC plants employing the animal dose-response estimates, which were applied to the 17 ppb of vinyl chloride (the average estimated concentration in the 5-mile radius of the plants). Both mathematical probability models were used. The results are tabulated in Table 18.

TABLE 18

Estimated Incidence of Cancer in Populations Living in the Vicinity of Vinyl Chloride-PVC Plants (Kuzmack and McGaughy, 1975)

Type of Effect	Cases per Year of Exposure	
	Linear Model	Log-Probit Model
All Cancer	11	0.1 - 1.0
Liver Angiosarcoma	5.5	0.05 - 0.5

Based on the linear model it was estimated that an incidence of 1 to 10 cases of liver angiosarcoma per year

can be expected in the exposed population living in the vicinity of vinyl chloride and PVC plants. The calculation using the log-probit model predicted an incidence rate which is 10 to 100 times lower. The estimates for all cancers were about twice as great in both cases. The uncertainties in extrapolation process to low doses are reflected in this wide range of estimated effects.

The vinyl chloride-related cancer incidence probability calculations by Kuzmack and McGaughy (1975) provide the best available quantitative estimate of the risk resulting from vinyl chloride exposure of a large segment of U.S. human population living in the vicinity of vinyl chloride-PVC plants. Recently published epidemiological studies indirectly support their conclusions. Brady, et al. (1977) investigated the annual incidence rate for angiosarcoma of the liver among residents of New York State (excluding New York City). The study indicates that direct exposure to vinyl chloride, arsenic, and thorium dioxide was a significant factor in the etiology of this type of cancer ($P < 0.02$); and that it resulted in its increased incidence by a factor of 2 over the expected annual incidence for the U.S. (0.25 per million for New York State vs. 0.14 per million for the U.S.). The important finding in this study was the diagnosis of five new cases of angiosarcoma of the liver in persons living in the vicinity of vinyl chloride polymerization and fabrication plants for 8 to 62 years prior to diagnosis of the disease.

The most recent report on this subject is a worldwide review of all cases of liver angiosarcoma in workers published by Spirtas and Kaminski in June, 1978. The conclu-

sions concerning the workers' age at diagnosis of the disease and the latency period, both of which appear to be increasing in recent years, are most important. Lloyd reported in 1975 that the median age at diagnosis was 44 years and the latency period from first exposure to diagnosis averaged 17 years. Spirtas and Kaminski (1978) reported 49 as the median age at diagnosis and a latency period of 21 years. It is probable that the initial cases may have had higher exposures of vinyl chloride and that the recent cases are due to more moderate exposures. It is also possible some variation is caused by statistical uncertainty in the age and latency parameter.

The concentration of vinyl chloride in water which is estimated to result in an excess lifetime risk of 10^{-5} can be calculated from the risk estimates for ambient air near vinyl chloride-PVC plants. It was shown that people breathing 17 ppb of vinyl chloride in air continuously have a lifetime risk of 10^{-5}. The assumption is made that the same daily intake via 2 liters/day of water will lead to the same risk and that fish bioaccumulate vinyl chloride 1.9 Fold. The air intake is 24 m^3/day x 17 ppb x 1 $\mu g/m^3$/0.387 ppb = 1.05×10^3 μg/day. If this intake comes from 2 liters of water, the vinyl chloride concentration of water would have to be $1.054/2 + 1.9(0.0187) = 0.517$ μg/l.

Insufficient information is available on the exposure levels and associated risk to man from vinyl chloride-contaminated water supplies. Toxicologic or epidemiologic data are not available in the up-to-date literature. From the available data, it is thought that the hazard is small in comparison to inhalation route of exposure.

There are insufficient hard data available on the vinyl chloride exposure levels of persons living in the vicinity of vinyl chloride/PVC fabricating plants and on the amount of the vinyl chloride monomer released in time from various plastic products.

There are some initial data on vinyl chloride concentration in food packaged in PVC containers. The food oils require a special attention; toxicologic data support this evidence.

Recent epidemiologic reports indicate that the median latency period for hemangiosarcoma occurrence in vinyl chloride-exposed workers is shifting to the right; and suggest that the recently diagnosed cases may have been due to lower exposures than the initial cases. This is an observation which - if confirmed -may have important consequences regarding the estimation of future risk for the population living in the vicinity of vinyl chloride/PVC plants, in addition to the workers.

Basis and Derivation of Criterion

Vinyl chloride is a well-known human and animal carcinogen. Several occupational epidemiology studies in highly exposed workers have reported excess rates of liver angiosarcoma and tumors at other organ sites. Animal experiments using both inhalation and oral routes of exposure have also induced liver angiosarcoma.

The recommended water quality criterion is calculated using the tumor incidence data from chronic rat inhalation studies. The validity of these incidence rates for humans was established by evaluating the cancer incidence in workers after accounting for their exposure.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Vinyl Chloride is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of vinyl chloride in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of vinly chloride corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish (2)	0 µg/l	5.17 µg/l	51.7 µg/l	517 µg/l
Consumption of fish and shellfish only.	0 µg/l	260 µg/l	2600 µg/l	26,000 µg/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document to the animal bioassay and human epidemlogical data summarized in Appendix I and in Tables 9 and 17 (as discussed in the document).. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000 , and so forth.

(2) Two percent of the vinyl chloride exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 1.9 fold. The remaining 98 percent of vinyl chloride exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of vinly chloride, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding vinyl chloride concentrations and, (2) occurring solely from consumption

of aquatic life grown in the waters containing the corresponding vinyl chloride concentrations.

Although total exposure information for vinyl chloride is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality cirteria formulation until additional analysis can be made. The criteria presented, therefore, assume an incremental risk from ambient water exposure only.

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Appendix I

Derivation of Criterion for Vinyl Chloride

In a previous report on risks to vinyl chloride in the ambient air (Kuzmack and McGaughy) the rat inhalation experiments of Maltoni were combined with occupational epidemiology studies to estimate risks to inhaled vinyl chloride. The result was that a continuous exposure of 17 ppb of vinyl chloride results in a lifetime risk of 10^{-5}. On the assumptions that the same daily intake of vinyl chloride via 2 liters of drinking water produces the same risk, and that fish bioaccumulative vinyl chloride to a small degree (BCF=1.9), the following calculation is used to find the water concentration giving a lifetime risk to 10^{-5}.

Intake of vinyl chloride via air is:

$24\ m^3/day \times 17\ ppb \times (1\mu g/m^3/0.387\ ppb) =$

$1.054 \times 10^3\ \mu g/day$

If this intake comes from 2 liters of water and ingesting 18.7 grams per day of fish and shellfish products, the ambient water concentration would have to be 1.054 mg/kg/day 2 + 1.9(0.0187) = 0.517 mg/l.